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Alternative Medicines

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INTRODUCTION

Although alternative medicine has the oldest healing practices, it is regaining popularity against a background of rapidly increasing technology in conventional medicine. For conventional health care practitioners, accepting the validity of alternative practices can be difficult, particularly because so little alternative medical training is provided at conventional medicine colleges and universities.

For pharmacy practitioners, herbal medicine presents a contradiction. Pharmacognosy, the study of natural product medicines, is a historical field of study in pharmacy. In addition, many conventional medicines are derived from herbs and other plants. However, in recent years, pharmacy has abandoned its "roots" in favor of clinical practice, and most pharmacists have little knowledge of herbals. No matter the level of pharmacist knowledge or bias on whether herbals can be helpful, the fact of the matter is that more patients are using them. This is sometimes at the risk of significant toxicity. All health care providers, but particularly pharmacists, need to develop a knowledge base of herbal medicines in order to best care for patients.

DEFINITIONS

Alternative Medicine

Often called "complementary and alternative medicine," this group of medical practices has also been termed "unconventional," "unorthodox," "unproven," and even "quackery."[1] Because these terms have significant negative connotations, terms such as "alternative medicine" are preferred. Alternative medicine is not one form of medicine, but rather a diverse group of health practices that are outside of what is considered usual or conventional by the medical establishment.[2] Alternative medicine spans the range of practices, from home remedies to manufactured products, from patient self-treatment to care by a skilled practitioner, from efficacious to potentially dangerous. Specific definitions of more common alternative medicine practices used in the United States are listed in Table 1.[1]

Herbal Medicine

Although alternative medicine encompasses a very broad range of practices (more than 150 in fact), the area of most interest to pharmacy practitioners is herbal medicine. Interestingly, there is no definition of "herb" in any federal legislation or in any Food and Drug Administration (FDA) regulation.[3] Definitions vary considerably depending upon the source. For example, botanists define an herb as a plant whose stem dies back in winter (vs. trees or shrubs). On the contrary, pharmacognosists define herbs as the aerial parts of plants (vs. seeds or roots).[3] The Herbal Trade Association, a group that has economic interests in this definition, defines an herb as a plant, plant part, or extract thereof used for flavor, fragrance, or medicinal purpose.[3] In any case, herbal medicine implies the use of the *whole plant or plant part* as a remedy, rather than a single, active constituent derived from a plant.

SIGNIFICANCE OF HERBAL USE

Prevalence of Use

Phone surveys were done in 1990 and 1997 by Eisenberg et al. to determine the prevalence of alternative medicine use in the United States. Over 1500 participants were surveyed in 1990, as well as over 2000 in the follow-up survey in 1997. The percentage of participants surveyed who reported using at least one form of alternative medicine in the preceding 12 mo was 34% in 1990 and 42% in 1997.[4,5] This is the oft-quoted "1 in 3 Americans use alternative medicine" statistic. Herbal medicine use rose from only 2.5% in 1990 to 12% in 1997, making it one of the fastest growing alternative medical practices used in the United States.[4,5]

Demographics of Users

According to the surveys conducted by Eisenberg et al., alternative medicine users tend to be educated, younger to middle-aged, female, and have chronic medical conditions. They self-refer 90% of the time, meaning

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Table 1 Complementary and alternative medical practices

Practice	Definition
Acupuncture	Ancient Chinese technique that uses needles to pierce the skin
	Taps into a grid of flowing energy ("qi") that controls organ function
Aromatherapy	Uses botanical oils and essences to treat both physical and psychological disorders
Ayurveda	"Life knowledge"
	Ancient Indian practice that uses diet, exercise, yoga, meditation, herbs, and massage to treat imbalances in physical, emotional, and spiritual harmony
Bioelectromagnetics	Study of living organisms and their interaction with electromagnetic fields
	Belief that magnetic fields penetrate the body and heal damaged tissues
Chiropractic	Practitioners use manipulation to treat disorders of the spine, joints, and muscles
Herbal medicine	Plants that are made into pills or extracts to prevent and cure physical and psychological disorders
Homeopathy	"Like cures like"
	Belief that very small doses of substances that would at high doses cause adverse effects can be used to cure those effects
	Preparations may be so dilute that the active ingredient no longer remains
Mindfulness meditation	Belief that the mind can influence health and control physiologic responses
Naturopathy	Relies on diet, fasting, massage, herbs, homeopathy, and other natural treatments
Osteopathy	Practitioners use manipulation to expedite recovery from disease or injury
	Practitioners also receive conventional medical training and prescribe drugs
Reflexology	Spots on the foot are massaged to stimulate specific organs
Therapeutic touch	Caregiver moves hands inches above the patient's body to realign disturbed energy fields or remove "blockages"

(From Ref. 1.)

that their primary care practitioners are not involved in the decisions to pursue alternative therapies.[4–7]

The use of alternative medicine varies with the patient population. For example, up to 80% of cancer patients report use of alternative medicine vs. one-third in the general population. Surveys also find that two-thirds use herbal medicine.[7–10] Interestingly, cancer patients do not abandon conventional therapies when using alternative medicine, with close to 90% using both conventional and alternative medicines together.[4,6,9] Particularly with herbal medicine use, this creates the potential for conventional drug interactions. In fact, in Eisenberg's[5] 1997 survey, 20% of participants admitted to using conventional prescription medications with herbal supplements. Because less than 10% of herbal medicine users are under the care of an herbalist, pharmacists are often the only health care providers who can help to avoid potentially dangerous adverse effects and interactions.[10] Similar to cancer patients, a large proportion (45%) of AIDS patients also report alternative medicine use.[11] Of those patients, two-thirds use herbal supplements, and most use alternative practices with their conventional HIV treatments.[11]

Reasons given by patients as to why alternative medicine is used include the following: the perception that conventional therapies are ineffective and/or toxic; frustration when no effective conventional therapy exists; the desire to take a more active role in their own care; distrust of conventional practitioners; and the belief that alternative practitioners focus on the whole patient.[6,10] Although most patients still use conventional medical practices with alternative medicine, only one-third tell their conventional practitioner that they are doing so.[4,5,8] This again means that the pharmacist may be the only conventional health care practitioner who is aware of both patients' conventional and alternative medicine use.

Cost

It is estimated that over $20 billion are spent each year on visits to alternative practitioners.[5] Sixty percent of patients pay all of these costs out-of-pocket, with only 20% of health maintenance organizations (HMOs) and third-party payers supplementing at least some of these health care costs.[5] It is also estimated that $1–5 billion are spent on herbal supplements per year, and interestingly, less than 5% of patients who use herbals report that they bought those products in a pharmacy.[5]

What Pharmacists Know

Given the recent rise in herbal supplement use and the potential dangers of misuse, one would expect that the pharmacy profession would be prepared to deal with public's need for reliable information on herbs.

Unfortunately, this is generally not the case. A 1998 survey done by the University of Mississippi found that only 2% of pharmacists felt confident in their herbal medicine knowledge.[12] Another survey in 1998 performed in North Carolina and Virginia included a 15-point test on five of the most common herbal supplements.[13] Of the 164 participants, 68% worked in a community setting and 74% sold herbals. However, the mean score on the 15-point test was only 6.3, indicating that pharmacists have inadequate knowledge with which to advise patients taking herbals.[13]

One would also hope that Colleges of Pharmacy would have increased the education they give to pharmacy students on herbal medicine, to prepare them better for the needs of consumers. This has also been quite slow to change. There is very little detailed literature in this area; however, a 1997 survey was done and asked Colleges about alternative medicine courses in the curricula. Although three-fourths responded that they taught about alternative medicine, only one-third of the courses were required, and less than 40% of content taught was about herbals.[12] Comparison of this statistic to a survey of breast cancer patients found that 71% of herbal users thought that herbals were "perfectly safe," a fact known to be untrue.[10] Pharmacists will not be able to help patients avoid harmful effects from herbals unless they are educated about uses, toxicities, and potential herb–drug interactions.

REGULATION AND OVERSIGHT

National Center for Complementary and Alternative Medicine

The federal government has had some insight into the need for a federal office to oversee dissemination of information on alternative medicine. Previously known as the Office of Alternative Medicine (established in 1992), the National Center for Complementary and Alternative Medicine (NCCAM) was established in 1998 as part of the National Institutes of Health.[1,2] The mission of NCCAM is to "give the public reliable information on the safety and effectiveness of complementary and alternative medicine," with an emphasis on clinical trial sponsorship.[2] The budget of the NCCAM has grown from $2 million in 1992 to almost $70 million in 2000, and almost half the budget is mandated to fund peer-reviewed grants.[2] The NCCAM also helps to disseminate information to the public, sponsors literature evaluations, and acts as an international liaison for alternative medicine. The NCCAM actually divides alternative medicine into seven broad categories: 1) alternative systems of medical practice (such as ayurveda and Chinese medicine); 2) bioelectromagnetics; 3) diet and nutrition (such as macrobiotics); 4) herbal medicine; 5) manual healing methods (such as chiropractic and therapeutic touch); 6) mind/body techniques (such as yoga and meditation); and 7) pharmacological and biological treatments (such as shark cartilage).[2] More specific information about NCCAM may be found at the website: http://nccam.nih.gov/.

Dietary Supplement Health and Education Act

One would assume that the federal government would also take a significant role in regulating substances (e.g., herbal therapies) that have the potential to cause significant harm. Although the FDA does want to hold many herbs to a higher standard, political pressure has led to the passage of legislation that makes herbal supplements more widely available with less oversight. This legislation is the Dietary Supplement Health and Education Act (DSHEA).

Prior to DSHEA, herbs were inconsistently regulated as drugs, foods, and/or food additives. Several events led to the passage of DSHEA. In 1990, 258 ingredients in over-the-counter drug products were banned for sale by the FDA due to inadequate efficacy data. Eighty-five of these ingredients were of herbal origin. Manufacturers responded by either pulling the products from the market or, more importantly, selling the products as "dietary" supplements.[14] This caught the attention of the FDA, and in 1993, the then Commissioner David Kessler publicly proposed that herbal supplements be held to the same standards as drugs, that is, be proven safe and effective or be removed from the market. These comments led to much public concern about continued availability of herbals, and many letters were written to members of Congress. The political pressure was great enough that in 1994, DSHEA was passed.

The DSHEA was a bipartisan bill cosponsored by Orrin Hatch of Utah and Tom Harkin of Iowa. First, it broadened the definition of a "dietary supplement" to include any product designed to supplement the diet that contained one or more of the following: a vitamin, mineral, herb, botanical, amino acid, or any metabolic constituent or extract thereof. To be removed from the market, supplements must be proven unsafe by the FDA. This is in contrast to drugs, where the burden of proof (both safety and efficacy) is on the manufacturer. Supplements must contain the labeling "Not evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent disease." They must also be labeled either "dietary supplement" or "herbal supplement," as well as have the common name, Latin binomial, quantity, and plant

part used on the label. Products may be sold as dietary supplements as long as no health or therapeutic claims are made. So, structure/function claims are permitted, and the label may state things such as "elevates mood" or "maintains cardiovascular health." Disease claims, however, are prohibited. For example, supplement labels may not state "treats depression" or "lowers cholesterol."[3,14]

Limitations of Regulations

There are several limitations that lead to potential for patient harm with the current regulation of herbals under DSHEA. First, botanical nomenclature is not standardized. Common names for herbals may vary depending on the region of the country. A single herb may have more than a dozen common names (e.g., echinacea), or one common herbal name may refer to several different species (e.g., yellowroot and snakeroot).[14] To avoid confusion, the American Herbal Products Association (AHPA) has published *Herbs of Commerce*, a text of more than 500 herbs with the preferred common name, Latin binomial, and appropriate synonyms.

Second, good manufacturing practices (GMPs) of herbal supplement manufacturers are not regulated by the FDA. This means that there is no guarantee that what is on the label of the supplement is actually what is in the bottle. An example of this is a study published by Gurley et al.[15] examining the ephedra alkaloid content of 20 herbal weight-loss supplements. Ten of the 20 supplements assayed (50%) had more than a 20% discrepancy between the actual ephedra content and the labeling. Four products also had significant lot-to-lot variation, up to 1000% of labeled ephedra content in one. Interestingly, one product contained no ephedra alkaloids at all.[15]

Third, safety assurance is the responsibility of the FDA, not the manufacturer. This means that the FDA must accumulate a significant amount of proof that something is unsafe before pulling it from the market. In addition, to help professionals, the AHPA has published *The Botanical Safety Handbook* that summarizes safety data of more than 600 herbs. However, there is no guarantee that any particular manufactured product is safe. An example is a recent recall of PC-SPES supplements by the FDA.[16] The PC-SPES is a combination of eight herbs marketed as a treatment for prostate cancer. It is known to have estrogenic activity, which is presumably how it affects prostate cancer.[17] However, laboratory analysis performed at the California Department of Health found that the recalled products were contaminated with warfarin.[16] The implications of this are that even if PC-SPES is thought to be safe, any given product could contain other potentially harmful substances.

Finally, efficacy of herbal supplements is difficult to establish. Many reported uses for herbs are hundreds of years old and anecdotal in nature. Because most herbal supplements cannot be patented, large pharmaceutical firms are reluctant to spend the money that is necessary to conduct randomized, placebo-controlled trials. To overcome this problem, in 1978, the German government established Commission E to evaluate the safety and efficacy of herbs. To date, more than 300 have been evaluated, and the monographs were translated into English in 1998. Unfortunately, most consumers do not have access to these monographs, and the language in DSHEA simply adds to the potential for patient harm, with structure/function claims leading to vague and potentially dangerous messages to consumers. For example, echinacea is often marketed as a supplement to "boost" the immune system. This may lead patients with HIV disease to believe echinacea would enhance their impaired immunity. Actually, the opposite is true: effects of echinacea may actually *decrease* CD4 cell counts in HIV patients, leading to increased risk of infection.[18]

COMMONLY USED HERBAL SUPPLEMENTS

Many dozens of herbal supplements are available to be purchased over-the-counter. Discussion of all these herbal supplements is beyond the scope of this article. Listed below is a brief discussion of each of the more commonly available and used supplements, including highlights of known active constituents, pharmacology, dosing, supporting clinical literature, adverse effects, and interactions with conventional medications. The known and potential drug–herb interactions are summarized in Table 2.[18–22]

Black Cohosh (*Cimicifuga racemosa*)

Black cohosh is also known as black snakeroot, bugbane, bugwort, rattleroot, and rattleweed. It should not be confused with blue cohosh, a uterine stimulant historically used to induce labor.[18] Black cohosh is used to treat menopausal symptoms, including hot flashes, excessive sweating, emotional lability, and sleep changes.[23] The exact active constituents are not known but are thought to include the *triterpene glycosides* (such as actein, 27-deoxyactein, deoxyacetylacteol, and cimicifugoside), *phytosterins*, and *isoflavones* found in root extracts.[18,23] For many years, practitioners thought that black cohosh must be estrogenic, but more recent animal and human data suggest that its pharmacology does not involve acting as an estrogen.[23] This was confirmed by a recent controlled trial in breast cancer patients with

Table 2 Reported and potential herb–drug interactions

Herb	Interacting drug or drug class	Effect
DHEA	Antidiabetic agents[a]	Decreased hypoglycemic effects
Garlic	ASA, NSAIDs	Additive antiplatelet effects
	Clopidogrel, ticlopidine	Additive antiplatelet effects
	Warfarin	Increased risk of bleeding
Ginger	ASA, NSAIDs	Additive antiplatelet effects
	Clopidogrel, ticlopidine	Additive antiplatelet effects
	Warfarin	Increased risk of bleeding
Ginseng	ASA, NSAIDs	Additive antiplatelet effects
	Antidiabetic agents	Additive hypoglycemia
	Clopidogrel, ticlopidine	Additive antiplatelet effects
	CNS stimulants, caffeine	Additive CNS toxicity
	Corticosteroids	Additive CNS toxicity
	Digoxin	Falsely elevated levels
	MAO inhibitors	Increased toxicity
	Warfarin	Increased risk of bleeding
Ginkgo	Anticonvulsants	Decreased antiseizure effects
	ASA, NSAIDs	Additive antiplatelet effects
	Clopidogrel, ticlopidine	Additive antiplatelet effects
	Warfarin	Increased risk of bleeding
Green tea	Warfarin	Decreased anticoagulant effects
Hawthorne	Antihypertensives	Additive hypotension
	Digoxin	Potentiation of (+) inotropic effects
Kava	CNS depressants, ethanol	Additive sedation, risk of coma
	Hepatotoxins	Additive hepatotoxicity
Licorice	Antihypertensives	Antagonism of hypotensive effects
	Corticosteroids	Additive mineralocorticoid effects
	Digoxin	Risk of toxicity due to hypokalemia
	Diuretics	Additive hypokalemia
Ma huang	CNS stimulants, caffeine	Additive CNS stimulation
	Digoxin	Additive toxicity
	MAO inhibitors	Hypertensive crisis
Melatonin	CNS depressants, ethanol	Additive sedation
St. John's wort	Cyclosporine	Decreased levels and decreased effect
	Digoxin	Decreased levels and decreased effect
	Indinavir, neverapine	Decreased levels and decreased effect
	MAO inhibitors	Increased risk of MAO toxicity
	Oral contraceptives	Decreased levels and decreased effect
	Simvastatin	Decreased levels and decreased effect
	SSRIs	Increased risk of serotonin syndrome
	Warfarin	Decreased levels and decreased effect
Valerian	CNS depressants, ethanol	Additive sedation

[a]Antidiabetic agents include drugs such as insulin, glipizide, glyburide, and metformin.
ASA = aspirin; NSAIDs = nonsteroidal anti-inflammatory drugs, such as ibuprofen, naproxen, and diclofenac; CNS stimulants include drugs such as pseudoephedrine, dextroamphetamine, theophylline, and caffeine; MAO = monoamine oxidase; CNS depressants include drugs such as benzodiazepines, barbiturates, and ethanol; SSRIs = selective serotonin reuptake inhibitors, such as fluoxetine, sertraline, and paroxetine.
(From Refs. 18–22.)

treatment-related hot flashes found no difference in efficacy when compared to placebo.[24] However, the compound was considered to be safe in these patients. No changes in luteinizing hormone (LH) or follicle stimulating hormone (FSH) levels were noted between the two groups, indicating limited estrogenic activity.[24] The most studied doses range from 20 mg to 40 mg twice daily.[18,23] Initial effects may be seen within 2 weeks, but maximal benefit

generally takes 8 weeks of continued therapy.[23] Black cohosh is quite well tolerated, with only mild gastrointestinal (GI) effects noted. Long-term data is not available, and patients should be advised to limit use to six months.[18] Again, the concern that black cohosh may stimulate breast or endometrial cancer cells by acting as an estrogen is not founded based on recent data.[23,24] However, this herb should be avoided in pregnancy as miscarriages have been reported. Black cohosh has no known herb–drug interactions.[18] However, postmenopausal patients should be advised that black cohosh is not a direct substitute for estrogen replacement therapy, as it has undetermined benefits for osteoporosis and cardiovascular disease.[23]

Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone is not truly an herb but rather a natural steroid product of the adrenal glands. In addition, DHEA is the steroid precursor to 50% of androgens in men, 75% of estrogens in premenopausal women, and close to 100% of estrogens in postmenopausal women. Levels peak between age 20 and 30, then decline approximately 2% per year thereafter.[25] Because levels are known to decline with age, DHEA is often marketed as an "antiaging" supplement. There are absolutely no clinical trials published examining this effect. In addition, DHEA levels are known to be lower in many chronic disease states, including some cancers, cardiovascular disease, systemic lupus erythematosis (SLE), Alzheimer's, and progression of HIV disease. Dehydroepiandrosterone has been studied in small trials as a treatment for fatigue in HIV patients as well as for treatment of depression in middle-aged patients and for SLE.[25] Replacement doses in patients known to be deficient (due to long-term corticosteroid use or chronic disease) are 20 mg–50 mg per day in men and 10 mg–30 mg per day in women.[25] Doses for the other indications listed above are much higher, ranging from 200 mg to 500 mg per day.[25] Adverse effects are directly related to increased androgen production and include acne, insomnia, irritability, and hirsutism.[18,25] Perhaps, the most serious potential adverse effect of DHEA is stimulation of hormone-dependent cancers such as prostate, breast, and endometrial. Because of this potential, patients with known risk factors or a personal history of these tumors should not take DHEA.[18,25] It has not been reported to cause herb–drug interactions. However, it is a mild inhibitor of the cytochrome P450 3A4 isoenzyme system and may increase concentrations of metabolized drugs to a minor extent.[18]

Echinacea (*Echinacea angustifolia, pallida,* and *purpurea*)

Echinacea has a host of other common names, including American coneflower, black Sampson, black Susans, comb flower, Indian head, Kansas snakeroot, purple coneflower, red sunflower, survey root, and Sampson root.[18] It is used as a nonspecific immune stimulant and has several active constituents. Caffeic acid derivatives and high-molecular weight polysaccharides stimulate phagocytosis of macrophages and natural killer cells. They also increase production of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1. In addition, echinacea contains alkylamides that have anti-inflammatory properties.[26] The portions of the herb used are the dried root or the fresh juice from the root and aerial parts. The form most commercially available is the dried root in capsules. Because the active constituents are not water soluble, tinctures and teas are not likely to be as effective.[18] The best form of echinacea is likely an alcoholic extract of the root, either 1:1 or 1:5 in 45% ethanol. Doses are usually 1 ml–2 ml taken 3–4 times a day. The most studied indications include prevention of viral upper respiratory infections (URIs) in patients at high risk, as well as adjunct treatment of URIs, to decrease severity of infection. The strongest data are with treatment, rather than prevention, and a recent review of randomized trials published since 1997 found two negative and three positive. The positive trials found that echinacea decreased the frequency, duration, and magnitude of URI symptoms.[27] For this indication, patients should be advised to begin echinacea at the onset of symptoms and continue therapy until 24 hr after symptom resolution.[26] For prevention, studies have examined taking echinacea daily for 8 weeks during the "cold and flu" season; however, this indication is not generally recommended due to inadequate data.[18] Adverse effects are rarely reported, although patients may experience allergic reactions.[26] There are also a few reports of immunosuppression with more than 8 weeks of continuous use, and long-term use should be avoided. There are no known herb–drug interactions with echinacea, but there are several herb–disease state contraindications. HIV patients should avoid using echinacea, because it may increase TNF-alpha levels, which in turn decreases CD4 counts. Also, due to the potential for immunostimulation, patients with autoimmune diseases should not take echinacea (e.g., multiple sclerosis, collagen–vascular diseases).[18,26] Of interest, there is one controlled trial in women who took echinacea during pregnancy. More than 400 women were monitored for pregnancy outcome: 200 who took echinacea and 200 who

did not. There was no difference in the rate of spontaneous abortion or the rate of fetal malformations, indicating echinacea may be safe for limited use during pregnancy.[28] No other herbal product has such conventional literature published for use and exposure during pregnancy.

Evening Primrose Oil (EPO, *Oenothera biennis*)

Evening primrose oil is named for the flowers on the plant that open in the late afternoon. It is also known as king's cure-all.[18] The seeds contain 7%–10% gamma-linoleic acid (GLA), an essential omega-6 fatty acid. The body relies on the metabolic conversion of linoleic acid to GLA, and this conversion is defective in a number of disease states, including fibrocystic breast disease, diabetic neuropathies, and various skin disorders (such as atopic dermatitis and eczema).[18] The EPO has been studied in numerous small trials for these indications as well as for premenstrual syndrome. Trials in various breast diseases have been positive, although it may take 6 mo or more to see effects. Doses range from 2 g to 4 g EPO (which is 200 mg–400 mg GLA) per day in 2–3 divided doses. Doses for neuropathy treatment are generally higher.[18] At all these doses, EPO is well tolerated, producing only mild GI upset and headache. Patients should take doses with food. In addition, EPO has no known contraindications and no reported herb–drug interactions.[18]

Garlic (*Allium sativum*)

The active component of garlic is formed when alliin, a compound in the bulbs, is converted by the enzyme allinase to allicin.[18] During food preparation, this conversion takes place when the bulbs/cloves are crushed. The conversion may also take place in the GI tract, although the conversion is reduced in the presence of stomach acid. Fresh garlic intake is considered to be the most efficacious way to consume this herb for disease–treatment indications, although many forms of tablets, capsules, tincture, and juices are available. For nonfresh intake, tinctures and oils should be avoided due to instability of allicin. Enteric-coated tablets, prepared by drying the crushed bulbs and then compressing them into tablets, are also likely effective, as they bypass the effect of stomach acid.[18] Garlic has been most studied for the treatment of dyslipidemias and hypertension. Its effects on blood pressure are not well substantiated; however, in a recent meta-analysis of 13 randomized trials, garlic was found to produce modest reductions (20%) in total cholesterol and triglycerides.[29] Doses used range from 600 mg to 900 mg per day, which is roughly equivalent to 4 g of fresh garlic cloves per day.[29] In addition, a recent review of 45 trials found not only reductions in total cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides with garlic therapy, but also noted decreases in platelet aggregation. No effects on blood glucose were seen.[30] Garlic has minimal adverse effects, with the exception of GI effects (such as heartburn and flatulence) and the characteristic body odor. Contact dermatitis has been reported with extensive handling of the fresh cloves.[18] Again, garlic inhibits platelet aggregation that may cause herb–drug interactions with other antiplatelet and anticoagulant drugs.[18]

Ginger (*Zingiber officinale*)

The part of this herb used is the root that contains 1%–3% gingerols. When the root is dried, the gingerols are converted to shogaol and zingerone, but the clinical significance of this conversion is not known.[31] The gingerols are thought to stimulate upper GI motility, similar to the effects of metoclopramide.[31] This gives rise to ginger's most common indication, that of an antiemetic. Ginger has no known central effects on the chemoreceptor trigger zone in the brain. Dosing for motion sickness and morning sickness is 1 g–4 g per day fresh ginger or 500 mg–1000 mg as dry powdered root. Daily intake is generally divided into 2–4 doses. For motion sickness, ginger has been shown to be superior to placebo and even to dimenhydrinate in some small trials.[31] A recent randomized trial in 70 pregnant women with morning sickness also found ginger to be superior to placebo for reducing both nausea and vomiting.[32] Ginger has also been studied in postoperative nausea/vomiting but with less positive results. It has also been marketed as a treatment for osteoarthritis, but the data for this indication are weak at best.[18,31] No significant adverse effects have been observed with ginger. It may be a mild inhibitor of platelet aggregation, and therefore, the potential for herb–drug interactions exist.[18] These antiplatelet data are not as strong as for garlic, ginseng, and ginkgo.

Gingko (*Gingko biloba*)

The ginkgo tree is also called the kew tree, maidenhair tree, and fossil tree.[18] It is the oldest known tree species, and the largest commercial farm of gingko trees is in Sumter, South Carolina. The most common indications for ginkgo are related to increasing mental capacity, as well as to treat cerebral and peripheral vascular disease. This may be due to touted benefits of flavonoids and terpenoids (gingkoloides and others) that may inhibit

platelet-activating factor, increase cerebral circulation, inhibit arterial spasms, decrease capillary permeability and fragility, and improve brain tolerance to hypoxia. They may also act as free radical scavengers.[18] It is recommended that extracts from the seeds and leaves be used that have been standardized to 24% flavonoids and 6% terpenoids. The most studied tablets contain 40 mg of this extract. Use for general improvements in cognitive function are not well studied; however, there have been several trials for Alzheimer's-type dementia. Doses from 40 mg to 80 mg 3 times daily have been shown to improve cognitive skills, although results may take 3 mo or longer to be seen.[18,33] In addition, a recent meta-analysis examined the results of eight randomized trials treating intermittent claudication with ginkgo 40 mg 3–4 times daily. This dose significantly improved pain-free walking distances.[34] The reported adverse effects of gingko include nausea/vomiting, diarrhea, and seizures with overdose or excessive intake of the seeds (rather than the leaves).[18] There have also been case reports of excessive postoperative bleeding, likely due to the antiplatelet effects of gingko.[35] Due to these antiplatelet effects, there is the potential for herb–drug interactions with conventional anticoagulant and antiplatelet agents.[18]

Ginseng

The herb known as "ginseng" is representative of the dangers of inconsistent nomenclature. There are actually three herbs that are known by this common name: American or western ginseng (*Panax quinquefolius*), Asian or Chinese ginseng (*Panax ginseng*), and Siberian ginseng (*Eleutherococcus senticosus*), a very different albeit related plant species.[18] For the purposes of this text, ginseng refers to both American and Asian, as they have very similar therapeutic and adverse effects. The active components in ginseng are 12 ginsenosides isolated from the root.[18] Ginseng is marketed to enhance both physical and mental performance, and certainly the ginsenosides are CNS (central nervous system) stimulants. However, data for the therapeutic effectiveness of these compounds are limited. A recent trial in 83 otherwise young healthy adults (mean age 26 years) compared two doses of ginseng (200 mg and 400 mg per day) to placebo.[36] There were no differences noted in psychological well-being.[36] Adverse effects reported for ginseng are numerous and include chest pain, palpitations, hypertension, headache, insomnia, irritability, nervousness, hypoglycemia, impotence, and GI effects (such as nausea, vomiting, and diarrhea). Reported and potential drug interactions are related to ginseng's antiplatelet and CNS stimulant effects.[18] Due to these adverse effects that occur more frequently than with other previously discussed herbals, ginseng should be used cautiously, particularly in patients with a history of cardiovascular or CNS disease.

Glucosamine/Chondroitin

Glucosamine is an endogenous aminomonosaccharide used in the synthesis of proteoglycans in cartilage, which are depleted in osteoarthritis.[37] Current conventional treatment of osteoarthritis is supportive only and includes treatment with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs decrease the pain and inflammation associated with the disease, but they do not change the overall disease process.[37] Glucosamine, on the other hand, may increase cartilage production, or at least slow breakdown, as well as provide mild anti-inflammatory effects.[37] Chondroitin is extracted from the cartilage in bovine trachea and may increase collagen synthesis in cartilage.[18] Short-term trials with each agent used individually have shown modest results compared to placebo and NSAIDs.[18] A meta-analysis of 15 randomized, placebo-controlled trials was positive overall in favor of glucosamine/chondroitin, but the authors remarked that bias was likely as almost all the trials were sponsored by the manufacturer.[38] They conceded that efficacy in osteoarthritis appears "probable."[38] Unfortunately, the additional benefit of chondroitin to oral tablets is minimal at best, because glucosamine is 95% absorbed but chondroitin has minimal oral bioavailability.[18] The combination is well tolerated, producing only mild headache, nausea/vomiting, and occasional rash.[18] The Arthritis Foundation does not recommend the use of this supplement, but due to few adverse effects, a trial in patients intolerant to other conventional analgesics would not be unreasonable. Doses are often weight-based and range from 1000 mg to 2000 mg per day, divided.[18] Unfortunately, there are no long-term studies published with this long-term condition. Animal data have reported hyperglycemic effects, so diabetic patients should monitor blood glucose levels closely.[18]

Grapeseed (*Vitis vinifera*)

Grapeseed extracts from the seeds of the herb contain flavonoids, as well as some essential fatty acids and tocopherols. The flavonoids are considered as the primary active constituents, inhibiting lipid peroxidation. Tocopherols, related to vitamin E, are also antioxidant in

nature.[18] The most studied patient population with grapeseed is cardiovascular disease patients, particularly patients with dyslipidemias. Doses range from 25 mg to 300 mg daily. No adverse effects or drug interactions have been reported for grapeseed, although conventional clinical data are limited.[18]

Green Tea (*Camellia sinensis*)

Green tea is made in a curing process that withers and then ferments the leaves of this herb before drying them. This process is thought to preserve the activity of the polyphenols contained in the fresh leaves. Most teas are standardized to contain 60% polyphenols, which are purported to have antioxidant, lipid-lowering, and potentially anticancer effects.[18] Green tea also contains 1%–4% methylxanthines, including caffeine.[18] Clinical trials looking at the efficacy of green tea are few, but it is thought that significant consumption (6–10 cups per day) is necessary to see effects.[18] A recent phase 1 trial in patients with refractory solid tumors found no objective responses with 5% stable disease.[39] The dose-limiting toxicities were caffeine-related, and the maximum tolerated dose was equivalent to 7–8 cups per day of green tea.[39] Dairy products may inhibit the polyphenols in green tea, so concurrent consumption should be avoided. The only reported adverse effects are rare allergic reactions. Patients should be advised, however, of the modest caffeine content of green tea, particularly because many herbal teas are "caffeine-free."[18] Green tea may contain significant vitamin K content as well; therefore, the effects of warfarin may be inhibited.[40]

Kava (*Piper methysticum*)

Kava is a member of the black pepper family and is also known as ava, awa, kew, sakaw, tonga, and yagona.[18] The root contains kavapyrones that inhibit the limbic system, and they are sedating and may elevate mood to a minor degree. Kava is marketed as an anxiolytic and as treatment for depression and insomnia.[41] Doses used range from 60 mg to 120 mg daily at bedtime.[18] Unfortunately, several potentially dangerous effects have been recently attributed to kava. Clearly, sedation, visual changes, and decreased motor reflexes are potential toxicities. Coma has even been reported with concurrent use of kava and alprazolam.[41] In addition, the FDA is investigating at least 25 cases in Europe of hepatotoxicity attributed to kava.[16] Caution should be exercised when using kava with other CNS depressants, especially benzodiazepines, or hepatotoxins. Kava does not appear to cause psychological dependence.[18]

Ma Huang (*Ephedra sinica* and *nevadensis*)

Ephedra has also been called Brigham tea, desert tea, herbal fen-phen, joint fir, Mexican tea, Mormon tea, natural ecstasy, popotillo, sea grape, squaw tea, teamster tea, and yellow horse.[18] The active component, ephedrine, was isolated in the 19th century and was used extensively in the 20th century in nasal decongestants and as a CNS stimulant. Extracts of ephedra seeds and stems contain 0.5%–2.5% alkaloids, not only including ephedrine, but also pseudoephedrine, methylephedrine, and norephedrine. All are CNS stimulants, with effects similar to amphetamines and caffeine.[18] Although ephedra is no longer available in conventional nasal decongestants due to the risk of toxicity, it is commonly found in many herbal weight-loss products. This is due to its ability to suppress the appetite and increase metabolic rate. Ephedra is available as capsules, tablets, teas, and tinctures. The FDA advises consumers not to take more than 24 mg in 24 hr and to limit use to no more than 7 days.[18] The primary problem with ephedra is the high potential for toxicity. It is a CNS stimulant, and as such, can cause anxiety, confusion, headache, insomnia, and irritability. These effects are greatly increased when ephedra is taken with caffeine. In addition, ephedra has significant cardiovascular effects, including reported hypertension, tachycardia, myocardial infarction, and cardiac arrest, usually when the labeled maximum daily dose is exceeded. These potentially fatal effects have been reported even in previously healthy young adults. A recent review of 98 events thought to be possibly or probably related to ephedra intake in a 2-yr period (1997–1999) found 47% cardiovascular effects (primarily hypertension, as well as palpitations and tachycardia), as well as 18% CNS effects, including strokes and seizures. Ten deaths were reported.[42] All of these adverse effects also lead to potential herb–drug interactions with other stimulant drugs. In addition, patients with glaucoma, cardiovascular disease, thyroid disease, psychiatric conditions, diabetes, or prostate disease should avoid using ephedra. Pregnant women should also not take this supplement due to the potential for uterine contractions and preterm labor.[18] The FDA is still investigating all reports of serious effects (more than 800 to date) due to ephedra and may ban this product from the market in the future.[18]

Melatonin (N-Acetyl-5-methoxytryptamine)

Melatonin is not an herb but rather is a naturally occurring hormone produced in the pineal gland from tryptophan. It is also commercially synthesized. Endogenously,

melatonin is released during sleep periods, and levels are low during the day.[18,43] As a supplement, melatonin has been most studied as a preventative/treatment for jet lag and as a sedative–hypnotic. For jet lag, patients are advised to take 5 mg daily at bedtime beginning three days prior to travel and continuing for three days after travel is complete.[18,43] Levels of melatonin decrease with age, so it has been studied in elderly patients with sleep disorders. This patient population is more sensitive to the effects of melatonin; therefore, they should start with lower doses, usually 1 mg–2 mg at bedtime.[43] Patients with liver disease should use melatonin cautiously, as clearance of the compound is impaired.[43] Adverse effects reported with melatonin use include headache, confusion, sedation, and mild hypothermia. Concurrent use of CNS depressants, including alcohol, should be avoided.[18,43]

Milk Thistle (*Silybum marianum*)

Milk thistle is also known as Our Lady's thistle, Mary thistle, Marian thistle, and St. Mary's thistle.[18] The active constituent, silymarin, has been isolated and the structure determined for many years. Only the fruit of the herb contains the active ingredient, 1%–4% as a mixture of three related compounds: silibinim, silidyanin, and silychristin.[44] Silymarin may act to stabilize hepatocyte membranes, as well as stimulate RNA polymerase, aiding liver regeneration after cell damage. It is also thought to be a free radical scavenger.[18] Interestingly, milk thistle is the only known antidote for poisoning by the "death cap" mushroom, *Amanita phalloides*. The dosing for this poisoning is intravenous silymarin, which is only available in Europe.[18] Milk thistle is also marketed and studied as a treatment for acute and chronic alcoholic and viral hepatitis, as well as a treatment for hepatotoxicity from drugs such as haloperidol and prochlorperazine.[44] Decreased complication rates have been observed in acute viral hepatitis, as well as improvement in liver function tests in alcoholic hepatitis. However, no survival benefit with milk thistle has been observed.[44] The most studied dose for liver diseases is 140 mg silymarin three times daily, which are 200 mg milk thistle extract doses standardized to 70% silymarin.[18] Teas should be avoided as a dosage form due to silymarin being practically water-insoluble.[44] Milk thistle has no known herb–drug interactions and causes minimal toxicity, including diarrhea and occasional allergic reactions. Milk thistle should be avoided in pregnancy due to its ability to cause uterine contractions.[18]

S-Adenosylmethionine (SAMe)

This is an endogenous substance produced from adenosine triphosphate and the amino acid methionine. It is naturally involved in a range of biological processes.[45] As a supplement, it is most studied in the treatment of depression, as well as treatment of liver disease. In a recent meta-analysis, doses of 400 mg–1600 mg per day were found to be superior to placebo and as efficacious as moderate-dose tricyclic antidepressants.[45] A few small trials in patients with liver disease have demonstrated improvement in liver enzymes with doses of 1600 mg per day or more.[45] Due to limited bioavailability, SAMe was previously only available intravenously. Enteric-coated tablets are now available as well, but bioavailability studies are lacking. Doses should be titrated, starting with 200 mg once daily and increasing by 200 mg increments every 1–2 weeks.[45] The SAMe is well tolerated, with only mild GI distress noted as an adverse effect and no known drug interactions.[45]

Saw Palmetto (*Serenoa repens*)

Saw palmetto is also known as the cabbage palm and American dwarf palm tree.[18] The ripe berries are thought to contain the active ingredients (perhaps fatty acids and sterols); however, the exact active components are not known.[18] Saw palmetto is mainly used in the treatment of benign prostatic hypertrophy[46] due to postulated inhibition of 5-alpha-reductase, the same mechanism as the conventional drug finasteride. The dose most studied is 160 mg twice daily. In a recent meta-analysis of 18 randomized trials, saw palmetto improved urologic symptoms to a rate similar to finasteride and better than placebo.[46] Saw palmetto is well tolerated, causing mild abdominal pain, nausea/vomiting, and occasional decreased libido.[46] Due to the risk of birth defects, pregnant women should avoid the use of saw palmetto.[18] No known herb–drug interactions are reported; however, saw palmetto will reduce prostate-specific antigen (PSA) levels. This test is used to screen for prostate cancer; therefore, men at risk of this disease should avoid saw palmetto due to the risk of a false negative result.[18]

St. John's Wort (*Hypericum perforatum*)

This herb is also known as St. Joan's wort, klamath weed, and goatweed.[18] It has historically been used for many purposes, but most recently it is marketed as an antidepressant. In fact, it outsells all conventional antidepressants in Germany. The active constituent is hypericin that seems to act as a weak monoamine oxidase

MAO inhibitor and a selective serotonin reuptake inhibitor (SSRI). Dopamine and norepinephrine uptakes are also mildly inhibited.[18] St. John's wort is available in many forms, as a tablet, tea, tincture, and the raw dried herb. For best results, a tablet standardized to contain 0.3% hypericin should be taken; Kira® by Lichtwer Pharma is the most extensively studied.[18] Randomized, placebo-controlled trials using 300 mg of St. John's wort three times daily have found it to be superior to placebo in mild to moderate depression. Response rates are generally regarded as inferior to conventional antidepressants, including tricyclic antidepressants and SSRIs.[47,48] In addition, St. John's wort is not without toxicity. Reported adverse effects include dizziness, headache, sleep changes, restlessness, dry mouth, and photosensitivity.[18] Perhaps most significant are the reported herb–drug interactions. St. John's wort is a significant inducer of the cytochrome P450 3A4 isoenzyme system, which is responsible for metabolizing up to 60% of conventional drugs. There are several case reports of clinically significant decreases is serum cyclosporine concentrations, leading to transplanted organ rejection.[49,50] Also, decreases in indinavir concentrations have been reported, which could potentially lead to HIV treatment failures and resistance.[51] Other drugs metabolized via 3A4, including warfarin, digoxin, oral contraceptives, and simvastatin could potentially have levels decreased by St. John's Wort.[18] Finally, because of its weak MAO inhibition and serotonin re-uptake effects, St. John's wort should not be taken concurrently by patients on MAO inhibitors or SSRIs.[18]

Valerian (*Valeriana officinalis*)

Valerian has also been called All Heal, amantilla, Baldrianwurzel, and setwell.[18] The root extract contains iridoid triesters (valepotriates) that stimulate the release of gamma-aminobutyric acid (GABA).[52] This pharmacology is similar to that of the benzodiazepine sedatives.[18] Animal studies confirm this pharmacology, as valerian attenuates benzodiazepine withdrawal symptoms in rats.[52] As a sedative/hypnotic, valerian doses range from 400 mg to 900 mg taken at bedtime. Placebo-controlled trials are small and have mixed results. Some have shown increased quality of sleep and decreased sleep latency, while others have shown no difference vs. placebo.[52] Data for using valerian as an anxiolytic are equally weak. Patients desiring to take valerian prior to an anxiety-producing event should be advised of the questionable efficacy and that the doses are much smaller than as a sedative, 100 mg taken 90 min prior to the event.[52] Adverse effects include sedation, visual changes, headache, rare allergic reactions, nausea/vomiting, and case reports of hepatotoxicity. Use with other CNS depressants, including alcohol, should be avoided.[18]

Potentially Unsafe Herbs

Any herb may be unsafe or cause serious adverse effects when used incorrectly. The herbs listed in Table 3, however, have been more commonly reported to cause serious or life-threatening effects. Many are on the FDA's official list of unsafe herbs.[18]

Many unsafe herbs are anticholinergic in nature, often due to significant hyoscyamine (and to a lesser extent, scopolamine) content. This includes belladonna, the nightshades, henbane, jimsonweed, and mandrake. These herbs cause a constellation of symptoms often referred to as "Hot as a hare, blind as a bat, dry as a bone, red as a beet, mad as a hatter." This includes confusion, hallucinations, agitation, elevated temperature, hypertension, tachycardia, mydriasis, dry mucous membranes, dry/flushed skin, and nausea/vomiting. Ultimately, respiratory arrest, seizures, and life-threatening arrhythmias can occur.[53]

One herb, the calabar bea, actually causes cholinergic toxicity (as seen with pesticide overdoses) due to the physostigmine content in the ripe seeds. This toxicity includes bradycardia and hypotension, potentially leading to cardiac and respiratory arrest.[18]

Several herbs have significant content of cardiac (digitalis) glycosides, including A Scotch broom, Canadian hemp, hedge mustard, Lily of the Valley, monkshood, wallflower, and foxglove, of which the conventional medication digoxin is derived. These herbs can cause bradyarrhythmias and heart block.[18]

Other potentially unsafe herbs have varying degrees of neurotoxicity, GI toxicity, and hepatotoxicity. Many cause multiorgan toxicity. Nux vomica contains strychinine in the seeds and bark. Jalap and castor bean are cathartic laxatives. Callamus, chapparal, and comfrey are potential hepatocarcinogens.[54] Autumn crocus contains colchicine, and lobelia has nicotine-like effects. All of these herbs should be avoided, and their high potential for toxicity re-enforces the idea that "natural" certainly does not always mean "safe."[18,53,55,56]

PATIENT ASSESSMENT AND COUNSELING TIPS

When assessing a patient who wants to begin an herbal supplement, both past medical history as well as concurrent conventional medication used should be taken into account for potential interactions, as discussed

Table 3 Potentially unsafe herbs

Harmful effects	Common name	Latin binomial	Toxic constituents	Serious adverse effects	Comments
Anticholinergic	Belladonna	*Atropa belladonna*	0.3%–0.6% hyoscyamine in leaves and root	Anticholinergic toxicity	Toxic effects with 5 mg–50 mg
	Bittersweet nightshade	*Solanum dulcamara*	Solasonine in stem and unripe berries	Anticholinergic toxicity	Toxic effects with ≥10 berries; fatal adult dose ~200 berries
	Black nightshade	*Solanum nigrum*	2% solasonine in stem, root, unripe berries	Anticholinergic toxicity	Less toxic than belladonna
	Henbane	*Hyoscyamus niger*	0.04%–0.28% hyoscyamine in leaves	Anticholinergic toxicity	More sedating than belladonna
	Jimsonweed	*Daturia stramonium*	0.1%–0.6% hyoscyamine in ripe seeds, leaves, flowers	Anticholinergic toxicity	Seeds may be chewed or leaves smoked as cigarettes
	Mandrake	*Mandragora vernalis*	0.4% hyoscyamine in root	Anticholinergic toxicity	More sedating than belladonna
Cholingeric	Calabar bean	*Physostigma venenosum*	Physostigmine in ripe seeds	Cholinergic toxicity	Chewing seeds releases more physostigimine
Cardiotoxicity	(Scotch) broom	*Cytisus scoparius*	2% tyramine and 0.01%–022% sparteine in aerial parts	(−) inotrope, quinidine-like antiarrhythmic	Toxic effects with ≥30 g raw herb
	Canadian hemp	*Apocynum cannabinum*	Cardioactive glycosides in root and aerial parts	Bradycardia, A–V block	Less cardiotoxic than foxglove
	Foxglove	*Digitalis purpurea*	Cardioactive glycosides in ripe seeds, leaves, flowers	Bradycardia, A–V block, miosis	*Digitalis ianata* is major source of digoxin in the United States.
	Hedge mustard	*Sisymbrium officinale*	Cardioactive glycosides in aerial parts	Bradycardia, A–V block	Avoid confusion with other mustard species
	Lily of the valley	*Convallaria majalis*	Cardioactive glycosides in root, flowers, leaves	Bradycardia, A–V block	Water from the cut flowers also toxic
	Monkshood	*Aconitum napellus*	Aconitine in root, leaves, flowers	Hypothermia, bradycardia, respiratory arrest	Fatal adult dose ≥2 mg; topical use also toxic
	Wallflower	*Cheiranthus cheiri*	Cardioactive glycosides in ripe seeds and flowers	Bradycardia, A–V block	
Neurotoxicity	Nux vomica	*Strychnos nuxvomica*	2%–5% strychnine in ripe seeds and bark	Hyperthermia, agitation, seizures	Toxic effects with 30 mg–50 mg; fatal adult dose 1 g–2 g
	Wormwood	*Artemisia absinthium*	Thujone in the volatile oil from leaves and flowers	Delirium, psychosis, renal failure, xanthopsia	Thujone related to camphor

GI Toxicity	Bloodroot	*Sanguinaria Canadensis*	4%–7% sanguinarine in root	Tissue irritation and necrosis with topical use	Poorly absorbed
	Castor bean	*Ricinus communis*	42%–55% castor oil and 0.1%–0.7% ricin in ripe seeds	Cathartic laxative	Chewing seeds releases the ricin
	Jalap	*Ipomoea orizabensis*	12%–15% polymeric ester glycosides in root	Cathartic laxative	
	Marsh marigold	*Caltha palustris*	Protoanemonin in fresh flowers	Skin blistering, mucous membrane irritation	Dried flowers have little toxic effect
	Queen's delight	*Stillingia sylvatica*	Diterpene esters in juice of root	Inflammation and mucous membrane irritation	
Hepatotoxicity	Calamus	*Acorus* spp: *A. calamus*, *A. amaericanus*, *A. angustatino*	β-Isoasarone in oil from root: calamus <10%, americanus 0%, angustatino > 80%	Potential hepatocarcinogen	Active component related to reserpine
	Chaparral	*Larrea trindentata*	Nordihydro-guaiaretic acid in leaves	Cholestasis, potential hepatocarcinogen	
	Comfrey	*Symphytum officinale*	0.03%–0.6% UPAs in root and leaves	Veno-occlusive disease, potential hepatocarcinogen	Safe for use topically to unbroken skin for <10 days
	Germander	*Teucrium chamaedrys*	Teucrin A in aerial parts	Liver necrosis	Safe for use in small amounts to flavor beverages
	Life root	*Senecio nemorensis*	0.01%–0.1% UPAs in aerial parts	Veno-occlusive disease, potential hepatocarcinogen	
Multi-organ Toxicity	Arnica	*Arnica montana*	Sesquiterpene lactones in flowers	Hypertension, arrhythmias, muscle paralysis	May be safe for topical use
	Autumn crocus	*Colchicum autumnale*	≥ 0.4% colchicine in flowers and ripe seeds	Renal and bone marrow failure, hepatotoxicity	Fatal adult dose 5 g of seeds
	Cotton	*Gossypium herbaceum*	Gossypol in seeds and root	Heart failure, inhibition of spermatogenesis	Small amounts of cotton seed oil in foods are safe
	Daffodil	*Narcissus pseudonarcissus*	Lycorine in bulb, leaves, flowers	Respiratory arrest, topical irritation	
	Lobelia	*Lobelia inflata*	6% lobeline in leaves and seeds	Hypothermia, anxiety, seizures, arrhythmias, respiratory arrest	Nicotine-like, toxic effects with 1 g; fatal adult dose 4 g
	Mayapple	*Podophyllum peltatum*	20% podophyllotoxin in root and resin	Ataxia, seizures, psychosis, coma, mucous membrane irritation, bloody diarrhea	Ripe fruits are not toxic; etoposide is a semisynthetic derivative

(*Continued*)

Table 3 Potentially unsafe herbs (*Continued*)

Harmful effects	Common name	Latin binomial	Toxic constituents	Serious adverse effects	Comments
	Mistletoe	*Viscum album*	2% viscotoxins in leaves, berries, branches	Delirium, seizures, hypotension, cardiac arrest	Lives as a parasite on the branches of other trees
	Poison hemlock	*Conicum maculatum*	Coniine in leaves, berries, flowers	Mydriasis, dizziness, respiratory arrest	Fatal adult dose 30 g berries or 100 g leaves
	Wahoo	*Euonymus atropurpureus*	Unknown toxic compound in root bark, seeds, berries	Tonic–clonic spasms, coma, hypotension, cardiac arrest	
	Wild cherry	*Prunus virginiana*	Amygdalin in leaves, seeds, stem	Headache, muscle spasms, coma, respiratory arrest	Converted to cyanide in the GI tract
	Wormseed	*Chenopodium ambrosioides*	80% ascaridole in distilled oil of seeds, berries, aerial parts	Vertigo, seizures, respiratory arrest, hypotension, cardiac arrest	Oil may explode when heated
	Yellow jessamine	*Gelsemium sempervirens*	Gelsamine alkaloids in root	Dizziness, mydriasis, seizures, bradycardia, muscle paralysis, respiratory arrest	Fatal adult dose 4 ml extract or 2 g–3 g root
	Yohimbe	*Pausinystalia yohimbe*	6% yohimbine in bark	Mydriasis, anxiety, tremor, α-2 adrenergic block with hypertension, cardiac arrest	

UPAs = unsaturated pyrrolizidine alkaloids.
(From Refs. 18, 53–56.)

before. Patients should be counseled to inform the pharmacist of all medications being taken, both conventional and otherwise. They should be told that herbals may be helpful or harmful and that limited efficacy data are usually available that is done in a controlled, scientific manner. If the pharmacy practitioner feels that the supplement is safe to be taken by the patient, then several counseling points should be stressed to maximize the potential of taking a quality supplement product. Multiingredient products should generally be avoided unless the patient is under the care of an herbalist. Labels should list both the common and Latin names, as well as the name and address of the manufacturer. It is likely better to purchase a supplement made by a reputable, well-known manufacturer who has a history of conforming to GMPs. The patient should be told to be aware of the different dosage forms available and that not all herbals work best when taken as a tablet. "Whole herb" products are generally ground plant parts and are not standardized at all. They should be avoided. Of course, patients should be cautioned to not believe every efficacy claim made for supplements. Finally, patients should be told to promptly report any adverse effects they think may be due to the supplement.

ALTERNATIVE MEDICINE RESOURCES

Of course, published review articles, clinical trials, and case reports can be found on Medline. To aid the pharmacy practitioner in evaluating the potential safety and efficacy of various herbal products, the following is a list of additional reputable resources.[57,58]

Textbooks

- *The American Cancer Society's Guide to Complementary and Alternative Cancer Methods* (American Cancer Society, 2000).
- *The Botanical Safety Handbook* (McGuffin, CRC Press, 1997).
- *Herb Contraindications and Drug Interactions* (second edition, Brinker, Eclectic Medical Publications, 1998).
- *Herbal Medicinals: A Clinician's Guide* (Miller & Murray, Haworth Press, 1998).
- *Herbal Medicine: Expanded Commission E Monographs* (Blumenthal, Brinckmann, Goldberg, Integrative Medicine Communication, 2000).
- *The Professional's Handbook of Complementary and Alternative Medicine* (Fetrow & Avila, Springhouse, 1999).
- *Rational Phytotherapy: A Physician's Guide to Herbal Medicine* (fourth edition, Schulz, Springer-Verlag, 2001).
- *Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals* (second edition, Robbers & Tyler, Haworth Press, 1999).
- *Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies* (fourth edition, Foster & Tyler, Haworth Press, 1999).

Periodicals

- Alternative Medicine Alert.
- Alternative Medicine Journal.
- HerbalGram (American Botanical Council).
- Journal of Alternative and Complementary Medicine.
- Journal of Natural Products (American Society of Pharmacognosy).
- Natural Medicines Comprehensive Database (The Pharamcists' Letter).
- The Review of Natural Products (Facts and Comparisons).

Web Resources

- Alternative Medicine Foundation Herbal Medicine (http://www.herbmed.org).
- American Botanical Council (http://www.herbalgram.org).
- American Cancer Society's Alternative and Complimentary Therapies.
- Herbal Research Foundation (http://www.herbs.org).
- HerbNet (http://www.herbnet.com).
- NAPRALERT at the University of Illinois at Chicago (http://www.pmmp.uic.edu).
- National Cancer Institute PDQs on Alternative Cancer Therapies (http://www.cancer.gov).
- National Center for Complimentary and Alternative Medicine (http://nccam.nih.gov).
- The Natural Pharmacist (http://www.tnp.com/home.asp).

CONCLUSION

Use of alternative medicine is on the rise, with herbal medicine being one of the fastest growing practices. Herbal medicines are not held to the same efficacy and safety standards as conventional medicines, but are rather sold as dietary supplements under the DSHEA of 1994. Limi-

tations of this legislation include: nonstandard botanical nomenclature, little guarantee of GMPs, the burden of safety being on the FDA rather than the manufacturer, and efficacy data lacking. Nonetheless, dangerous adverse effects and herb–drug interactions are being reported with increasing frequency. Current pharmacy practitioners have not received formal training in herbal medicine, yet they need to be familiar with herbal uses, dosing, toxicities, contraindications, and potential drug interactions. This is necessary to help patients who choose to use supplements safely. Echinacea, garlic, ginseng, ginkgo, St. John's wort, ma huang, and valerian are among the most commonly used supplements, but there are many others readily available with potentially harmful effects. Fortunately, in addition to conventional periodicals, a number of reputable herbal texts and journals are available to provide the pharmacy professional with reliable herbal drug information.

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